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Description

to become viscous and study

TECHNICAL FIELD

DISCLOS - JETHS BUSENTON

This invention relates to β-lactam antibiotic-containing tablets and a method of producing the same. More particularly, it relates to tablets of the above variety which can be orally taken either as such or, in taking by, for example ithe its aged who have difficulties in swallowing eas a dispersion available upon dropping the same into water in a glass for self. to disintegration; and to almethod opportry line same at the state of the same and polypoper and to almethod opportry before the same at the how good celf-disintegraling piny rates and can be produced by a conventional method. Further more, the inventor rotter that when granulation is performed using attained is ADD/ORHDATARNOUS REPORTED TO THE PROPERTY OF THE PROPER rolution of artitivation isopropyl alcohol, facilities anowing befrer dispers bury upon self-mainteg, alton can be obtained. Racticularly in Europe, and America, where β-Jactam antibiotics such as extirmed and entire administered gen-. າາ "ules or tablets; ::: have to be considerably large in size. When 400 mg potency caps the e capsule size y acult patients reaches approximately. No. 0, so that not only patients have ""fices - ficult to take they become reluctant to take them or get a repulsive sensation ingly are largethe case of tablets, too 400 mg potency: training con-LACON DE MOST arequa binder spronetly together with one. besic opression to

The corobians and or dimitaking -יוני, חלי כי ~ theme?" patients on the

Theref tablet size a a dosage for simply dropped of advanced age u tegration" as used he. 🔩

unticu. Is in swallowing the dosage form as such. The expression "rapid self-disings is that when the preparation is dropped into a glass containing a liquid such as water, the tablet form spontaneo.; collapses generally within 3 minutes, preferably within 1 minute, so that said preparation can be orally taken in disperuing form without awaiting long before taking.

res from rapid suffdisines.

It is indeed easy to produce hables capable of sent disintegrating very rapidly by incorporating an effervescent agent comprising a combination of sodium hydrogen carbonate and tartaric acid, for instance. However, when such tablets are orally taken, they give off-bubbles in the oral cavity, so that patients feel a discoinfort or an unnecessary sensation of anxiety. For securing a good shelf-life in a humid environment, it is necessary to use a moisture-proof packaging Lisping the dosage form which the present invention is material, which increases the production cost. Therefore, mulation enabling very rapid self-disintegration without intended to provide, it has been a tough problem to find the aid of any effervescent component.

For producing 8-lactam antibiotic-containing table in the form of a dispersion resulting from self-dicir 0281200 B (corresponding Japanese patent ar to 70% by weight, based on the weight a first disintegrator and 2 to 20% h a second disintegrator.

However, said first disinte tion of a binder component stantially nil. This is becage process for producing is employed which co tured ith a ne aid of a are formed inevitably & , for tableting of is a pac-

Meanwhith table name of Figinoxin S been granted: Saich Land hence is vere largerar e Moc Bacitumes orally taken, give a bit. it thus becomesoned.... tion levels and thus suited for tab a problemes idea marriely the

be easily ingested as they are and be also ingested a technolo y is described in European Patent EP Koho S63-301820), which comprises adding 24 crystalline cellulose or microfine cellulose as tuted hydroxypropylcellulose or the like as

> tablet size. In addition, the proporon the antibiotic, hence is subsintegrating properties. In the an integrity of the artefact se and kneading the mixe a resulto large lumps 👳 to provide granules 👵

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DISCLOSURE OF THE INVENTION

QUART (AQUARC 5)

5	- It an attempt to develop a method obtinizioving the rate of self-disintegration of tablets and at the same and infinitely the same, the present inventor made investigations concerning the disintegrator species do be used the level of addition the configuration and the method of integration the binder addition the synthetic sweetener particle size (and the method of integrating the same, among others and, as a result, the inventor invented β-lactam antibiosic confining tablets which are small size of the same and the same same same same same same same sam	3
10	show good self-disintegrating properties and can be produced by a conventional method. Furthermore, the inventor found that when granulation is performed using ethanol, isopropyl alcohol or aft aqueous solution of ethanol or isopropyl alcohol, tablets showing better dispersibility upon self-disintegration can be obtained. The plactam anaber 1979 sining registes of this area stributed or anaber 1979 sining register of are placetared.	GY.
	antibiotic, 1 to alice and the same and the	
	have to be considerably large in size. Smen 400 mg putency caper use, bushquis where prioritished and interesting the prioritish content and the prioritish motion for the prioritish content and the prioritish c	ž (
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20	the granulation (composed the perconate, of the release of the passages Turing Second to the passages Turing Turi	
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	mulas spowy approximantement and respect to the second sec	
	of advanced age or children have a difficulties in swallowing the dorage form as such The expression "rapid entrene	- 59
25	regration" as used herein means that when the preparation is dropped into a glass containing a riquid such as water,	
	the tablet form spontaneously collapses generally winin 3 minutes, preferably with CPTUS so that said or specific	
	can be orally taken in dispersion to m without awaiting long before taking.	
	it is indeed easy to produce lablets caperale of self-disintegrating very rapidly by incorporating an efferyoscent	
	agent comprising a combination of sodium 1999 can be and tarraric acid, to instance However, when such table	98
30	lets are grally taken, they give of 13 to 100 the car cavito so that panents feet discontible or an unnecessary sense-	
	Con of anxiety. For securing a good shelf-life in a hunid anxironment, it is necessary to use a moisture-proof packaging	
	material, which increases the production cost. Therefore water 00 10 cosage from which the present invention is	
	intended to provide, it has been a touch problem intended to provide at the been a touch problem intended to provide. It has been a touch problem intended to provide at the been a touch problem.	
35	the aid of any effervescent component	
33	For producing β-lactam antibiotic-containing table be easily ingested as they are and be also ingested	
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	a second disintegrator.	
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	Bon levels and thus suited for abl designed the second state of th	

EP 0 890,359 A1 2 92

The tablets' of this invention further gontain binder as an essential constituent. The addition of a binder has an adverse effect on the self-disintegrating properties of tablets, hence is not desirable from the self-disintegration viewed to point. However, the production of tablets without adding any binder give such inconveniences as mentioned heroimbens at fore.

The inventor of this invention made investigations in search of binder species which would not give adverse effects on the self-disintegrating properties of tablets as well as investigations concerning the addition level thereof. As preferred binders, there may now be mentioned, for example, polyvinylpyrrolidone, hydroxypropylcellulose, preferably low-viscosity type (L-type) hydroxypropylcellulose, hydroxypropylmethylcellulose; methylcellulose, starch, pregelatinized continued starch, partly pregelatinized starch, income graphic, daytin, pullular, and the like. Among these binders, polyvinylpyrrolidone, hydroxypropylcellulose and hydroxypropylmethylcellulose, are more preferred, and polyvinylpyrrolidone is most preferred. When these binders are used in an amount of 0.5 to 2% by weight, preferably 0.8 to 1.5% by weight, on a personal tablet basis/tablets which can self-disintegrate repidly can be produced by a conventional production method. Onston

Since β-lactam antibiotics, for example cefixime and cefdinir, have a strongly bittler taste, it is necessary to add at expending synthetic sweetener in cases where tablets are to be taken in the form of dispersions after self-distribution in water, and the instance, though this is necessary in cases where tablets are to be taken as such.

As regards the synthetic sweetener addition level, which may vary according to the synthetic sweetener species and the active ingredient β-lactam antibiotic, the sweetener is incorporated in tablets generally in a proportion of 0.5 to 15% by weight, preferably 1 to 10% by weight.

The commercial synthetics westerer products are generally small, i.e. less than 150 µm, in mean particle size, with particle 'not smaller than 150 µm, accounting for at most 4%, of the whole incorporation of size products markedly reduced the rate of disintegration of tablets. To improve the disintegration rate, the prior art entitions a method which is comprises incorporating a large amount of an excipient such as microcrystalline callulose. However, incorporation of a large amount of such excipient according to said method results in an increase in tablet size, thereby making the tablets difficult to take with ease. The present inverted found that when the particle size of a synthetic sweetener and light anhydrous silico acid. Tydiated silicon diexide or the like is added, the rate of disintegration can be improved, namely prevented from retardation.

As a result, an invention was made of miniaturized tablets which can be easily taken as such and, when dropped into water in a glass, can rapidly self-disintegrate, enabling administration thereof in dispersion form.

When such a synthetic sweetener as saccharin, a salt thereof (e.g. saccharin calcium, saccharin sodium), cyclamic acid or a salt thereof (e.g. sodium cyclamate, calcium cyclamate, alimonium cyclamate) is used, said sweetener is required to be not less than 150 µm in mean particle size, preferably not less than 150 µm in particle size. In the case of a sweetener capable of producing a satisfactory bitter masking effect in small amounts, for example aspartame, it is not always necessary that the mean particle size be not less than 150 µm, since the disintegrability of tablets is little affected.

The synthetic sweetener may be incorporated either in the form of crystalline grains having a mean particle size of not less than 150 µm or in the form of a granulation product meeting the particle size requirement as obtained by wet granulation from the powder form small in mean particle size or by wet granulation or dry granulation from such powder together with a color additive and/or microcrystalline cellulose or a like excipient.

The granulation product containing light anhydrous silicic acid or hydrated silicon dioxide in addition to a synthetic sweetener can be produced by mixing the synthetic sweetener with 1 to 30% by weight, relative to the synthetic sweetener weight, of light anhydrous sillcic acid or hydrated silicon dioxide and granulating the mixture in the conventional manner, if necessary using a binder and/or one or more observables in common use. It was found that in the case of granulation products containing a synthetic sweetener together with light anhydraus silicic acid or hydrated silicon dioxide, the particle size is not critical, with the result that the self-disintegrating p found i waver adversely affected even when the mean particle size is below 150 µm. As regards other ingred ance micronized producing the tablets of this invention, the same ingredients or additives as used conventionals is pyrrolidone, toped preparations may be mentioned. Thus, in addition to the above-mentioned synthetic swaying under flowing air mailic sweetener, excipients such as microcrystalline cellulose, lactose, mannitol, starch, c. ... ownt annydrous silicic acid, hydrated silicon dioxide, etc., lubricants such as magneticile steamparticle sets with etc., flavoring agents and other agents may be incorporated Onless the self-disintegrating properties in inversely affected. When the β-lactam antibiotic has a large particle size, it may be ground prior to use. In this case, however, wet or dry granulation is required to improve the powder flowability in the step of compression. resticked pulyvinylpytrolidene

In a preferred process for producing the tablets of the present invention, the acoverage disintegrator and billider, optionally together interingredistrictly explanated by a conventional method, the above-mer/long asynthetic synthetic synthetic

When, in the above production process, water is used for granulation in the granulation step, tablets with good self-

EP 0 890 359 AT

disintegrating properties are generally obtained. In this confrection, the inventor of this invention further found that when ethanol risepropyl alcohol or a mixture of water and ethanol or isopropyl alcohol is used for granulation; tablets with good self-disintegrating properties and with very good dispersibility upon allowing dispersion in water can be obtained. The concentration of the aqueous solution of ethanol or isopropyl alcohol, which is suited for use, is 3 to 99% (vol-The intention of the inventory made investigation of a finite (emulov) and of the property made investigation of the property race<mark>d bin</mark>oerą, tiere indy now be me<mark>ntioned, fot dxs</mark>nąle, pogwnytycolidopa, tydrozypiopy<u>loelistosa, prefera</u>dly loci Fireosity type (Lityce) hydroxyp: spyloeilulose, hydroxypropylmethyloeilulose, met ytoeilulos**ti tyllepi (Lityce) hydroxypropylmethyloeil**ulose, met ytoeilulos**ti tyllepi (Lityce)** The thus sold and a series of this invention are small in dize. For example, a tablet the thus sold and a series of this invention are small in dize. For example, a tablet the thus sold and a tablet containing about the series of this invention are small and a tablet containing about the series of the series containing 400 mg potency (about 449 mg) of cetixime may wellon not more than 650 mg and a tablet containing 300 nor mg potency (about 307 mg) of certiful not more than 450 mg. They can be crally taken as such with each, When they sign are to be taken by the eged, for instance, complaining of some difficulty in swallowing, in an acueous dispersion form, the tablets can be racidly disintegrated and dispersed in water. Moreover, the use of ethanol, isopropyl alcohol or an aqueous solution of ethanol or isopropyl alcohol tor, granula, Moreover, the use or emanufactured to a second to the control of t Test Example 1 (Disintegrator effect). The weight of contracts the second of the secon 15% by weight, preferency 1 to 10% by ive at . T. W. Esta elotinar. Section 1. Unit Call has beautiful facilities bulk substatics; nucromyst. "Inecollulose managethe According to the formulation and molecular facilities and substatics in the substatics of the collulose managether." According to the formulation and molecular facilities with a substatic properties with the substatic disintegrators, light aphydrous silicic acid and magnesium stearate, taken in the respective specified preportions, were edublishmatic argainant argainant of an excuser such as microcorporate designation of the such as microcorporate designation of leng (2) fiction to limit 000, to missing of the limit of betailing the process of table size, thereby making the smm. And the smm borism evode attitude to the smm. And the smm of the size of the si using a Japanage Pharm Soneja disintegration tester but without using any committee per mit ute of basket using a descending. The distribution can be improved, namely provented from Figure 2. Sets of the provented from the categories and distribution can be improved, namely provented from felling the categories and distribution can be improved. As a result, an invention was melle of win aturized **tablets which can be easily laken** as such and, wheild roppord And water in a glass, orn rapidity self-clur, **egreta, enebling Pdklaj**stration thereor in disr^{©a}lion form. When such a synthetic sweepr(conered off 004) 6.844 or a salt thereof (e.g. sodium cholamate, carollini cycl ornaloy: (mulcos relado ad, said oviesiener is and or a salt thereoi (e.g. sodiu ารดุมโกษร์ to be not less than 150 Jun เก เกษอก par,inle **ย.8.6** pi **ค่อการังในห้อวษาแผ้วเขาแล้วขา** gole size in its case mple aspertome, it is of a sweetener capable of produkting a sotisfactory biggsymskan,, effect in small r not always necessary that the meen particle size be not less than 160 jum, shifter elfil a abaider to ville : anhydrous silicic acid The synthetic eve etenor may be not reporated eiter in the form of crystalling trainers mulean rmean particle size of it as obtained by wet not less than 150 am or in the M granulation from the powder form small in mean of 1818 see or by wer granulation or iion from such gowder regether with a color additive anchor microcrystalling cellulose or a time exciptent ulientr it is all nortible. The granulation product contening light enhydrans choic acid or hydrated silicof yo the syrthetic sweet sweetener i≾a be produced by mixing the symheric sweetener.with 1 → 30% by weld IBOO TOWN POR POT THE ener weigm, of light amy cous sliids and or hydraled slicor, doxide and granualts ward sold of facility manner, if necessary using a sinder analor one of more ou exaib rapiles barant Disintegration tinie (min.) granulation products o netoeffs violateviols i ing to eld 對原 copie to e ic alektaj ere oribuk e sevitiob**1:3:1:3** ieiberop od vánji enominskom notine to report 2 if of notine raantioned. Thus, in ac Starch hic antrydroup sitioir .ylcallu.a. >sodijum ters emapo principal When the Uttil ture Law-substituted | Caroxy, opyticellutosa other **agents m**ay the n behaces at notification Crosslinked polyvinylpyrrolidone a tables of the present invection, the enfauthorist for assoring penetral i labler which colitain low-cussituit a receyor py relief copy questinked polyto fine to fir Trie? th conventions method, the above-man liquid view statistics in the and the entropy of the control o

When, in the above promised procest [Jester is used for granulation is the granulation step, \$20, \$20 he with mind carl-

combine mixture is subjected to velocimu.

Test Example 2 (Binder study)

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According to the formulation shown below in Table 3, cefixime bulk substance micronized by a pin-type mill, microcrystalline cellulose and one of the binders, legether with 50% (by volume) ethanol; were granulated in a high speed shear mixer, followed by drying under flowing air at 40°C for 17 hours and sizing through a 500-µm sieve. The granules sieved out were mixed with low-substituted hydroxypropylicellulose, light anhydrous silicic and and magnesium stearate, in the respective specified proportions, followed by compression on a single-punch tablet machine, to give tablets each having the specified weight and a diameter of 11 mm.

The tablets produced by the above method were evaluated for disintegration time under the same conditions as in Test Example 1. The disintegration time data thus obtained are shown in Jable 4 Apply 15 years

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1	e ∄abl	e 3	alaisate i	nuigenbelv
Cefixime	1,4	i	.448.9 (400 m	
Microcrystalline cellulose			38,9 _{nunisc}	rinedus- 3
Binder	0.00	mus	4.9 (14.6)	
Low-substituted hydroxypr	opylcelli		38.9	isio:
Light anhydrous silicic acid	Ì	An same	1.2	-
Magnesium stearate) :		5.9	
Total			538.7 mg (54	18.4 mg)
		1.000	<u> </u>	

	activing the ingentiation of the		and the second second second second second second	m inch see see se management and	remeter was peterner
•	0.6		Table 4	(mr 931 × eris ai	S. cohana calcina (maan pa
	Binder	108 17 480 45	% addition leve in mg)	(weight Disinteg	Seconario calcresia (min.)
	Polyvinylpym nocengemulb ni nemode v oski elom Hydroxyprop Hydroxyprop		ີ່ ຂັບດ່າງຢູ່9≹4.9) ດີເຮັກ ເຄີນເຮັກ ຄົ້ 0.9 (4.9)	tolets orzd. Us a bif lin calcium and fi ling traccom larc	ning the state of
Tes crys	As is evident from Table roxypropylmethylcellulose texample 3 (Synthetic swift According to the formula stalline cellulose, low-sub anol, were granulated in a using a 500-µm sieve. The	4) the tablets produce disintended in the particle size where particle size where the size	ed by using poly grate tapidly study) no one fable 5, cetixime to ylcellulose and po yer, followed by d	vinylpyrrolidone, leady the area open of a series of a	by a pin-type nill, micro- ther with 50% (by volume) at 40°C for 17 hours and siz- ic acid, magnesium stearate,
Exa pre	pared in Example 2 to be	ater herein or the gra mentioned later here hing to give tablets e	nulated mixture on the interest of the interes	if saccharin calcium a live specified proportion recified weight and a common control of the con	nocharin calcium prepared in and light anhydrous silicic acid ons, followed by compressing diameter of 11 mm.

cars and choisened to be an insight of the beat some The whole was alloying to stand for 5 min-Care Held vice de graphe and 20 million warear placed in 1. 56 on percuri. Clearfor self or Cotagram of Them, the beacher was shaken portly for caming and therepher allowed to staire for Cininute.

Test Example 1. The disintegration time data thus obtained are shown in Table 6.

or a leave hat province	aneral signa	AcTable 5 Year Coaling	Old March 5
The state of the s	SEC. 102. 1048.25	AL MEDICAL CONTRACTOR OF THE PROPERTY OF THE P	18 F 4,014 B, 3

1. a	La Company designation vol. of	A 4 9 (A /A /O Frag potency)	edit. In less interes e amentals
Tale aftern and the rate of	Cefixime	The Company of the	ratta i kulondi i berah kidawan da Kalambari di banyak iki maseth
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, ,	Polyvinylpymoltoona การพราชาธิ	s b:4.9.៦.៩ ខណៈខេត្ត ៤ ១៣ ៤ :	,इ.स.च्याकातांका वसी अवस्था असी
	Light anhydrous silicic acid	1.2	
	Magnesium stearate	5.9	
	Strawberry powder flavor	7.5	multo 1
	Saccharin calcium or	popular Agentians gentle	Private Re
	granulated saccharin calcium	20.0	A CAMPANA A CAMP
		5582 mg × 500 0 00 100	and the second
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	6.9	3. 3. 3. 3. 3. 3. 3. 3. 3. 3. 3. 3. 3. 3	the street of
	7.28.7 mg (649.4 mg)		
	Land	3 M	

Mean disintegration time Synthetic sweetener (min.), n = 63.0 Saccharin calcium (mean particle size < 150 μm) 0.6 Saccharin calcium (particle size 150-840 µm) Saccharin calcium-light anhydrous silicic acid mixture granulated (particle size 75-500 1:3:1 30 20. AA. 20

As is evident from Table 6, the tablets produced by using the saccharin calcium not less than 150 µm in particle size or the granulated mixture of accharin calcium and light anhydrous silicic acid are positively shorter in disintegration time than the tablets produced by using the commercial saccharin calcium smaller than 150 µm in mean particle size.

Test Example 4 (Influence of the composition of the solution for granulation on the dispersibility of tablets)

A 2,200 ml portion of water or an aqueous solution of ethanol was used to granulate a mixture of 4,566 g of cefixime bulk substance micronized by a pin-type mill, 405 g of microcrystalline cellulose, 405 g of low-substituted hydroxypropylcellulose and 50.6 g of polyvinylpyrrolidone in a high speed shear mixer and, after drying under flowing air at 40°C for 17 hours, the granulation product was sized using a 500-µm sieve. The granules signed out were mixed with 50.6 g of light anhydrous silicic acid, 101.2 g of magnesium stearate, 75.9 g of strawberry powder flavor and 202.6 g of saccharin calcium (particle size: 150-840 jum), followed by compressing on a rotary table; machine to give oblong tabless รัฐภาครั้งสูงนั้งวัน ค่อสุดเรียกรี และคุรสัน การโกกาม อรี่นอกพาโดย วิที่เล่น แต่และพร้อ each weighing 579 mg.

ion weigning are mu. as well as for dispersibility for use in dispersion form.

Example it to be murphy for tellow in the context of the subtractive and the relation and the modifical titles and Disintegration time

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The disintegration time evaluation was made in 1,000 ml of water (20 ± 1°C) using a Jaconese Pharmacopeia disintegration tester, but without using any disk, with 30 cycles per minute of basket ascending and descending. ହିଁ । ଜି.ଲି.ଗ୍ରିଡ଼ି ନ୍ୟ **be** j s.on a cit s an cinc mit enge di**eb ed** । ଏହା ମାଞ୍ଚିତ ଅଞ୍ଚିତ

o contra de desta de la contra d

Dispersibility after standing of dispersions prepared

One tablet was dropped into 20 rnl of water placed in a 50-ml beaker and the whole was allowed to stand for 5 minutes for self-disintegration. Then, the beaker was shaken gently for stirring and thereafter allowed to stand for 1 minute,

Was wire out to a second

followed by observation of the appearance.

After your Time of a compagnetial or one of the desire of the second of the contract of	face an elder, protable	
600 St. 1	Table 7	nedů uziš-nině – hej
grr, s ;	Disintegration time (sec.)	Dispersibility after stand-
Granulation using 50% ethanol	39	ata a re a munann
Granulation using 10% ethanol	ลา 150 นกาล หล ือเกิบเล ระธิส	rd exel)ca) r a violat niv.db :
Granulation using water	62	box yrisowie
Flemoxin Solutab 500 (commercial product) 46	b

- a: Wholly uniform in color, substantially without any precipitate.
- b : A supernatant and a slight amount of a precipitate.

The tablets derived from the grapules prepared using ethanol are still better in dispersibility after standing as com-The tablets derived from the granules prepared using water.

pared with those derived from the granules prepared using water.

pared with those derived from the granules prepared using water.

Test Example 5 (Disintegration test)

conselled to the of all and it encohern enters in taken to table 2. Test preparations A: Tablets produced in Example 1 to be mentioned later. B: Tablets produced in Example 7 to be mentioned later. C: Tablets produced in Example 8 to be mentioned later. s uchemication and hydrated alligen dicade wirte glower together in a ratio of the and then water was and early

Testemethod Long plant as the real factor of the re The disintegration time evaluation was performed in distilled water at 20 ± 10 with 4 cycles per minute of basket ar The disintegration time evaluation was pendimbed in the Japanese Pharmacopeia (42th edition) under a scending and descending, using an apparatus prescribed in the Japanese Pharmacopeia (42th edition) under a scending and descending, using an apparatus prescribed in the Japanese Pharmacopeia (42th edition) under a scending and descending using an apparatus prescribed in the Japanese Pharmacopeia (42th edition) under a scending and descending using an apparatus prescribed in the Japanese Pharmacopeia (42th edition) under a scending and descending using an apparatus prescribed in the Japanese Pharmacopeia (42th edition) under a scending and descending using an apparatus prescribed in the Japanese Pharmacopeia (42th edition) under a scending and descending using an apparatus prescribed in the Japanese Pharmacopeia (42th edition) under a scending and descending using a scending using usin

Disintegration Test.

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- B: 1.30 minutes
- C: 1:02 minutes

The disintegration test results indicate that the test preparations A to C of this invention each shows good disintegrability it, and the low and worker to the time and an army and the state of the section of another and the section of the se

EXAMPLE

ingale i etanolid in ab tenti mambe etimo. Water was added to saccharin calcium and the mixture was granulated by a conventional method, followed by drying, sieving and sizing to give saccharin calcium granules not less than 150 µm in particle size. 0.00 and the bard tech

According to the formulation shown below, micronized cefixime bulk substance, microcrystalline cellulose, low-substituted hydroxypropylcellulose (L-HPC) and polyvinylpyrrolidone were weighed and mixed together, water was then added, and the mixture was granulated. The granulation product was dried under flowing air at 40°C for 17 hours and then sized using a 500-umisieve. The granules sieved out were mixed with magnesium stearate, light anhydrous silicic acid, strawborry flavor and the above-mentioned granulated saccharin calcium according to the formulation shown below, followed by compressing on a single-punch tablet machine to give tablets each having the specified weight. and endiced sent ECO andeve. The drainwas have a made a think does im should brist any draw

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	MICIONIZEG CETIXIM	DUIK SUDStanc	. '	448.9 mc	(400 mg polency)
	Microcrystalline cell	lulose (Avicel™ PH1	01; Asahi Chemical Indi	ustry) 38.9 mg	L 30 COM

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Table 8 (continued)

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L-HPC (LH-21; Shin-Etsu C	hemical)	38.9 mg
	1 01	4.9 mg
Polyvinylpyrroligone (Kollida Light anhydrous silicic acid	on™ 30-BASE) no (Sea) erre nobe getreaid (Aérosil™; Tomita Seiyaku)	1.2 mg
Magnesium stearate	EC.	lenerie 1845 phas incitation C
Saccharin calcium (not less	than 150 μm in particle size)	20.0 mg เอกลูสิต 3%0 f คาโลน คะ เวลโนกมาร์.
Strawberry flavor	1.6	7.5 mg
Total 6	100) (40-	586.2 mg

Example 2

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Saccharin calcium and light anhydrous silicic acid were mixed together in a ratio of 20:1 and then water was added.

The resultant mixture was granulated by a conventional method, followed by drying and sizing to give a granulated mixture of saccharin calcium and light anhydrous silicic acid (75-500 µm in particle size):

Then, tablets were produced following the procedure of Example 1 except that 21 mg of the above granulated mixture was used in lieu of 20 mg of saccharin calcium (Example 1, Table 8).

Example 3

Saccharin calcium and hydrated silicon dioxide were mixed together in a ratio of 20:1 and then water was added.

The resultant mixture was granulated by a conventional method, followed by drying and sizing to give a granulated mixed ture of saccharin calcium and hydrated silicon dioxide (75-500 µm in particle size).

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Then tablets were produced following the procedure of Example 1 except that 21 mg of the above granulated mixture was used in lieu of 20 mg of saccharin calcium (Example 1, Table 8).

Example 4

Tablets each centaining 400 mg (potency) of cefixime were produced in the same manner as in Example thexcepter that L-HPC of Example 1 (Table 8) was replaced by the same amount of crosslinked polyvinylpyrrolidone (KollidonTM CL; assume 8.5.): A second 0.5.1:8

Example 5

Tablets each containing 400 mg (potency) of cefixime were produced in the same manner as in Example bexcept that polyvinylpyrrolidone of Example 1 (Table 8) was replaced by the same amount of hydroxypropylcellulose (HP.Gr.Lip Nippon Soda).

Example 6

Tablets each containing 400 mg (potency) of cefixime were produced in the same manner as in Example 1 except that polyvinylpyrrolidone of Example 1 (Table 8) was replaced by the same amount of hydroxypropylmethylcellulose that polyvinylpyrrolidone of Example 1 (Table 8) was replaced by the same amount of hydroxypropylmethylcellulose (TC-5R** Shin-Etsu-Chemical).

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Example 75% of Discovering grid. At wide a below as with conquirous little of the region grade and an entiting the bound

According to the same formulation as that shown in Example 1 (Table 8)? midronized cefixime bulk substance, microcrystalline cellulose, L-HRC and polyvinylpyrrolidone were weighed and mixed together, 50% aqueous ethanol microcrystalline cellulose, L-HRC and polyvinylpyrrolidone were weighed and mixed together, 50% aqueous ethanol was added, and the mixture was granulated. The granulation product was dried under flowing air at 40°Q for 17 bours, was added, and the mixture was granulated. The granulated out were mixed with magnesium stearate, light anhydrous and then sized using a 500-μm sieve. The granulated saccharingaleium prepared in Example 1 (not less than 150 μm in parsilicic acid, strawberry flavor and the granulated saccharingaleium prepared in Example 1 (not less than 150 μm in particle size) and the resultant mixture was compressed on a single-punch tablet machine to give tablets having the same ticle size) and the resultant mixture was compressed on a single-punch tablet machine to give tablets having the same composition as that in Example 1 (Table 8).

facrocrystatine cariolose (Artoolif PH of Charical Industry) 38.3 mg

Example 8

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	<u> </u>		
	Polyvinyapyrrolidone: (Kallidon-Sa)) anno a dour reas a fare a men	and the steel of the second of	J. Jr.
,	Light anhydrous silicic acid (Aerosil)	0.9 mg	
	Magnesium stoafale en interpretant production and and and order to recent trees	A r leas A A MO and go con grant and as a	
	Saccharin calcium (not less than 150 µm in particle size)	15.0 mg	
	Strawberry flavor	5.6 mg	
•	FOR MINISTER CONTROL OF STATE OF AN ADDRESS OF STATE OF S	TAPAS W. Constantial Services	
	Total	and the second contract of the second contrac	
Claims		63-301020, A (Gisterber 8, 1988 (08.	
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Category	Citation of document, with indication, where appropriate	riate, of the relevant passages	Relevant to claim No.	
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14	December 12, 51995 (12. 12095) Claim; page 2, right column, page 3, lower left column, li	lines 7 to 13;	Australia or practica se a sons erop to or unit oc	ergera. Loseti
Further	documents are listed in the continuation of Box C.	See patent family annex.	miel Jih barnalo sa Id	de A
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July 5, 1994 (05: 07: 94),
Claim; page 2, left column, line 35 to right
column, True 20; page 3, left column, lines 20
to 25 (Family: none) : 150**019**: 1160 ering in receipt of JP, 58-109419, A (Beecham Group Ltd.) June 29, 1983 (29. 06. 83), Constant State Column, Line 21, 1983 (29. 06. 83), Claim; page 2, upper right column, Line 2, 1983 (20. 06. 1983), Claim; page 2, upper right column, Line 4 & EP 80867 (1983), Claim; bus Res November 1984 (20. 1983), Claim; bus Res November 1984 (20. 1984), Claim; bus Res November 1984 (20. 1984 JP, 50-140623, A (Shin-Etsu Chemical Co. Ltd., III The), (Washington The), (Washington The Claim; page 2, upper left column, line 16 to page 3, upper right column, line 19 & US, 4017598, A "General Techniques for New Pharmaceutical Preparation Development Systems - Bases and Filling Material (in Japanese) " edited by Sadao Iguchi, R & D Planning, July 12, 1985 (12. 07. 85), p. 417-418, 432,436 Old DA YOFELIAN LION TVEDZBYRETNE DYTEAT THANKS. "Drug Handbook (in Japanese) 5th edition" TO Abstract Edited by Osaka-fu Hospital Pharmacists Assoc., A p and thing, effereers and fillegy mor hands a power as a reid at a seed and participated agreement as a substanting of the committee of the

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